

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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|---|--|--|---|
| To: BRADFORD G. ADDISON BARNES & THORNBURG LLP 11 SOUTH & MERIDIAN STREET INDIANAPOLIS, IN 46204 | | DOCKETED FOR <u>Response / Comment</u> BY <u>[Signature]</u> DATE <u>3/18/05</u> CHECK'D BY _____ DATE _____ | PCT WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1) |
| Applicant's or agent's file reference 29010-75970 | | Date of mailing _____ (day/month/year) 02 MAR 2005 | |
| International application No. PCT/US04/32401 | | International filing date (day/month/year) 01 October 2004 (01.10.2004) | Priority date (day/month/year) 03 October 2003 (03.10.2003) |
| International Patent Classification (IPC) or both national classification and IPC IPC(7): C07D 205/085, 201/08; A61K 31/397, 31/4178, 31/422, 31/4025 and US Cl.: 540/364, 363 | | | |
| Applicant SERENIX PHARMACEUTICALS, LLC | | | |

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input checked="" type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| | |
|--|--|
| Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230 | Authorized officer Mark L. Berch <i>[Signature]</i> Telephone No. (571) 272-1600 |
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/32401

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

- ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☐ in written format
☐ in computer readable form

c. time of filing/furnishing

- ☐ contained in international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/32401

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 24-27 and 29

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 24-27 and 29 are so unclear that no meaningful opinion could be formed (*specify*):

Under PCT Rule 6.4(a), these claims have improper multiple dependency, because these claims are multiply dependent on claims, e.g. claim 23, which is itself multiply dependent.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐

has not been furnished

☐

does not comply with the standard

the computer readable form

☐

has not been furnished

☐

does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/32401

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|------------------------|-----|
| Novelty (N) | Claims <u>1-23, 28</u> | YES |
| | Claims <u>NONE</u> | NO |
| Inventive step (IS) | Claims <u>NONE</u> | YES |
| | Claims <u>1-23, 28</u> | NO |
| Industrial applicability (IA) | Claims <u>1-23, 28</u> | YES |
| | Claims <u>NONE</u> | NO |

2. Citations and explanations:

Claims 1, 4, 13, 20-23, 28 lack an inventive step under PCT Article 33(3) as being obvious over WO 97/30707. See Formula I on pages 3-4. Note example 161, corresponding to R4 = styryl, n=0, R1=A=H, A' = t-butyloxy, R3 = choice 1 with R10 as phenyl. Note also Example 162, corresponding to R4 = styryl, n=0, R1=H, A = trifluoromethyl-benzylamino, A' = t-butyloxy, R3 = choice 1 with R10 as phenyl. The utility is the same. The claim 28 synthesis appear in the scheme on page 38. The sole difference is that applicants have an extra methyl group, R2 = methyl. Compounds that differ only by the presence or absence of an extra methyl group are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. See also MPEP 2144.09, second paragraph.

Claims 1-23, 28 lack an inventive step under PCT Article 33(3) as being obvious over WO 03/031407. See Formula I on pages 2-3 and in particular, Formula III on page 16, and the species of Tables 1-15. These include mono-substituted amino choices (e.g. Table 2, next to last species) and disubstituted amino, e.g. Table 1, species 3. See also Scheme I on page 26 for the synthesis. The sole difference is that applicants have an extra methyl group, R2 = methyl. Compounds that differ only by the presence or absence of an extra methyl group are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. See also MPEP 2144.09, second paragraph.

Claims 1-23, 28 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/32401

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-23, 28 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims are indefinite for the following reason(s):

Claim 28 is garbled. The final product has R4 in it but the starting materials do not. Thus, the starting materials do not match the final product.

1. In A and A', "substituted" with what?

2. The purpose of the last choice for R5 and R5' is unclear. This R⁶R⁷N-(C₂-C₄alkyl) choice appears to be identical to the previous R⁶R⁷N-(C₂-C₄alkyl) choice.